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# Enhancing Respiratory Medication Adherence: The Role of Health Care Professionals and Cost-Effectiveness Considerations

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**Learning objectives**:

1. To identify different types of non-adherence in asthma/chronic obstructive pulmonary disease (COPD) patients.

2. To understand how to apply effective communication styles to discuss non-adherence.

3. To target and tailor adherence-enhancing interventions in order to optimize cost-effectiveness.

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**Adherence to medication comprises a multiphased temporal process involving (1) initiation of prescribed therapy, (2) implementation as prescribed, and (3) subsequent persistence. Medication adherence remains suboptimal in most patients with long-term respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). Interventions have been shown to effectively improve treatment initiation, implementation, and persistence when delivered at the health care professional level or the system level, but demonstration of the cost-effectiveness of these interventions is necessary to ensure their widespread use. This review summarizes how health care professionals can intervene to improve medication adherence in patients with asthma and COPD, provides some examples of effective primary care interventions, and illustrates some of the challenges to optimal implementation arising from cost-effectiveness modeling. Improving adherence is shown to be an economically viable treatment option for patients with asthma and COPD, but there are differences in the health economics pertaining to each condition and setting that can affect whether an intervention is considered cost-effective. Targeting adherence interventions at patients with the greatest to gain, and tailoring them to individual patient needs, may help to optimize cost-effectiveness ratios and improve the probability of positive reimbursement decisions, systemwide implementation, and resultant health benefits.**  **(J Allergy Clin Immunol Pract 2016;4:835-46)**

***Key words:*** *Asthma; COPD; Medication adherence interventions; Initiation; Implementation; Persistence; Health care professionals; cost-effectiveness*

Adherence to asthma and chronic obstructive pulmonary disease (COPD) medication is central to achieving the desired treatment outcomes, but epidemiological studies suggest adherence remains suboptimal in most patients.[1] Adherence—a term that comprises (1) initiation of prescribed therapy; (2) implementation of therapy as prescribed (correct dose, inhalation technique, and frequency); and (3) persistence (obtaining refills to maintain adherence over time)—can be affected by many factors,[2] including patient and societal determinants.[3] Numerous studies have assessed the role of the patient (eg, their health beliefs, proficiency, and comorbidities)[4,5] and specific treatment aspects (eg, dosing regimen, inhaler type, and adverse effects)[6-9] with respect to adherence to asthma and COPD medications; far fewer have explored the effect of system-level determinants, such as the relationship between adherence and clinician-patient interactions or the organizational structure of health care (eg, consultation time or co-payment).

System-level determinants may, at least in part, result in limited uptake of medication adherence interventions in routine care. In many countries a key requirement for applying of medical interventions is reimbursement, which often necessitates demonstration of the cost-effectiveness of the intervention[10] and a supporting health care policy. Interventions must be complex enough to be effective, but simple enough to allow them to be scaled up and adopted in routine care. A cost-effectiveness analysis provides insight into the trade-off between financial investment in health care interventions and the degree of health improvement offered. A structured assessment can inform policymakers of the value of interventions before their broad uptake.

The role of health care practitioners is one of the main adherence determinant "domains" identified by the ASTRO-LAB Group (see article "Mapping the asthma care process: implications for research and practice" in this issue[11]). In this article, we discuss roles and actions that different health care providers can take to support medication adherence. We review a number of clinician-delivered interventions that may improve adherence to asthma and COPD medications. We also discuss system-level cost considerations and health economic assessment of adherence interventions for both conditions and consider how these may affect their uptake in routine care.

## THE ROLE OF PRIMARY HEALTH CARE PROFESSIONALS IN OPTIMIZING ADHERENCE

Because most patients with asthma and COPD are managed in primary care, interventions that general practitioners, nurses, or pharmacists can implement within routine care have the opportunity to reach the greatest number of patients with respiratory conditions.

### Structured assessment in consultations

In asthma, use of structured frameworks such as the SIMPLES (Smoking status, Inhaler technique, Monitoring, Pharmacotherapy, Lifestyle, Education, Support) approach can help to identify self-management problems and empower patients through standardized holistic assessment, avoid unnecessary medication escalations, and guide referrals to specialist care.[12]

Standardized holistic assessment suggests a dynamic consultation, facilitating dialogue between the clinician and the patient, exploring all aspects of the impact of asthma on the individual and vice versa, and ending with shared decision making concerning management. A number of components of the SIMPLES approach are relevant to supporting medication adherence—at each step of the adherence pathway. For example, correct *Inhaler technique* is integral to the successful delivery of respiratory medications[13] and a key cause of unintentional poor medication implementation. Technique varies substantially between devices, with most patients (and their clinicians) unable to consistently demonstrate correct inhaler use.[14,15] Clinicians should have knowledge of a range of devices so that they can tailor the device choice to the needs and characteristics of the patient, minimize use of different device types (to facilitate more accurate therapy delivery),[13,16] and teach, assess, and, where necessary, rectify inhaler technique each time the patient is reviewed.

*Monitoring* of symptoms and lung function by the patients can improve their ability to identify a deterioration in their level of

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*Abbreviations used*
*COPD- chronic obstructive pulmonary disease*
*FACI- facilitated asthma communication intervention*
*ICS- inhaled corticosteroids*
*RCT- randomized controlled trial*
*SIMPLES- Smoking status, Inhaler technique, Monitoring, Pharmacotherapy, Lifestyle, Education, Support*

control, prompt remedial actions (eg, trigger avoidance), and may also help patients link poor adherence to poor control, thus minimizing unnecessary medication escalation cost and potential treatment adverse effects.

Regular review of *Pharmacotherapy* and medication use in a systematic fashion can improve health outcomes.[17] Consultations should include a standardized assessment of patients' execution of each step in the adherence pathway, that is, confirmation of initiation, subsequent implementation as prescribed, and medication continuation. A patient-centered approach (which can be defined as "care that is holistic, empowering [which] tailors support according to the individual's priorities and needs"[18]) is highly relevant for assessing and supporting medication adherence. Where any aspect of adherence is considered to be suboptimal, an open, nonjudgmental exploration of the possible reasons for this should be conducted in partnership with the patient to elicit and work with patients' opinions, concerns, and expectations that impair adherence.[19] It is important to tailor medication dose to the specific needs and medication attitudes of the patient with clear instructions for upward/downward titration.

Adherence cannot be achieved by an unprepared patient. *Education* on how the disease and treatment(s) work and how and why to use medication is crucial to adherence. Consultation time is often perceived as a barrier to successful patient education, but recent research suggests this need not be the case.[20]

Although originally developed for use in asthma, the SIMPLES consultation model can also be adapted for use in COPD management. With respect to adherence, in COPD, *Pharmacotherapy* is somewhat more complex than in asthma. Although bronchodilation is the backbone of all treatment regimens,[21] there has been a historical trend to use high-dose inhaled corticosteroids (ICS) within COPD. High doses may impact medication implementation and persistence because they can increase the risk of unintended effects such as pneumonia or diabetes.[22,23] Similarly, persistence may be reduced by COPD patients' poor perception of the effectiveness of ICS treatment.[24]

## Concordance and shared treatment goals

The term "concordance" refers to the extent to which physicians and patients share a common perception, for example, of symptoms or clinical problems.[25] A shared understanding allows clinical management decisions to be more successful; treatment regimens tailored to individual patient's needs and preferences enhance good disease control.[26] For patients, concordance can increase their engagement and subsequent implementation of their prescribed treatment regimen. For physicians, concordance can help with disease monitoring, identification of nonadherence, and reduction of undertreatment/overtreatment. At present concordance appears suboptimal; for example, studies report poor concordance between patients' and physicians' perceptions of, and impact of, common COPD symptoms,[27] and between physicians and caregivers' understanding of prescribed maintenance therapy regimens in children with asthma.[28]

## Effective health care professional communication

Even where there is an established physician-patient relationship, patients can be reluctant to ask for additional information or to discuss nonrespiratory issues to avoid "wasting" the clinician's time.[29] Yet such issues (eg, lifestyle concerns, medication attitudes, and beliefs) can strongly influence patients' disease management.[30] Thus, it is important for clinicians to use empathy and relevant communication approaches (eg, open questions and attentive listening) to build trust and support full and honest discussions.

There is a large body of research on effective communication techniques for clinical consultations.[31,32] A systematic review has identified a number of verbal and nonverbal physician behaviors that appear to be associated with better interpersonal relationships with patients, improved patient understanding of health care advice, and their subsequent medication implementation (see Table I).[33] At the end of a consultation, inviting patients to repeat ("tell-back") the information that has been shared with them provides an opportunity to appraise patient comprehension and a means to correct, clarify, and reinforce key messages. Patients have been shown to prefer the use of the Tell-Back-Collaborative approach where patients are asked, in a patient-centered manner, to restate what they understand in their own words; for example, "I can hear you're worried about [this treatment]. I've given you a lot of information; it would be helpful for me to hear your understanding about [this treatment]." This approach contrasts with alternative strategies, such as Yes-No evaluations (eg, "I've given you a lot of information. Do you understand?"), or Tell-Back—Directive approaches (eg, "It's really important that you do this exactly the way I explained. What do you understand?").[34]

## Engaging with medication beliefs of patients

Given that noninitiation, suboptimal implementation, and poor persistence/early discontinuation of asthma and COPD medication is common, guidelines understandably encourage general practitioners to address medication adherence with their patients at regular intervals.[35] Yet many physicians are unsure about how to carry out effective adherence counseling[36] and uncertain of how to ask patients about adherence behaviors sensitively, so as to obtain reliable answers. Indeed, the specific wording used to ask patients about their medication use can be key to ensuring accurate patient reports. In 85 adult patients with asthma, the 3 questions detailed in Table II were strongly associated with actual adherence (measured by electronic monitoring), but the commonly used Morisky self-report questionnaire was only moderately associated with actual adherence.[37]

## Patient-centered approaches to supporting adherence

Once poor adherence has been identified, the next logical step is to provide the patient with effective adherence support. Patient-centered techniques, such as motivational interviewing, can help clinicians to elicit patients' views, beliefs, and concerns about their disease and its treatment, or other medical matters. Understanding patients' attitudes, beliefs, and concerns can help physicians to work with the patient to develop feasible health action plans centered on patients' personal goals. A set of simple, evidence-based support tools, drawing on motivational interviewing principles, has been developed to guide primary care clinicians in providing patient-centered adherence (implementation and persistence) counseling

**TABLE I.** Physician behaviors associated with positive and negative patient outcomes in primary care[37]

| Communication behaviors associated with positive patient outcomes | Communication behaviors associated with negative patient outcomes |
|---|---|
| Friendliness and courtesy | Formal, antagonistic, directive, or dominant physician behavior |
| Attentive listening | High rates of biomedical questioning |
| Empathy (expression of appreciation of a patient's situation) | Interruptions by physician |
| Statements of reassurance and support | Physician irritation or nervousness |
| Patient-centered strategies (eg, encourage patient's questions/allow patient's point of view to guide end of visit) | Tension |
| Positive reinforcement (expression of encouragement concerning patient's actions/self) | One-way information flow from patient to provider |
| Humor (relief of tension) | Expression of opinion during physical examination |
| Psychosocial talk (ie, asking about problems of daily living, social relations, feelings, and emotions of patient) | |
| Counseling for psychosocial issues | |
| Explanation | |
| Orienting the patient during physical examination | |
| Summarizing | |
| Health education and information sharing (eg, discussion of treatment effects or sharing medical data) | |
| Talking at the patient's level/using clarifying statements | |
| **Nonverbal communication behaviors associated with positive patient outcomes** | |
| Head nodding | |
| Forward lean | |
| More direct body orientation (ie, physician's body facing rather than turning away from patient) | |
| Uncrossed legs and arms | |
| Symmetrical position of the arms (eg, both arms hanging straight down) | |
| Less mutual gaze | |

(Figure 1).[38] Application of these approaches in routine primary care was shown to increase clinicians' confidence in counseling patients with asthma on adherence with preventer therapy; it also increased the frequency with which counseling was provided. Goal-setting record cards can be provided as a written reminder of patients' personal goals and chosen action strategies.[39] An evidence-based model of the clinician-patient partnership has been developed for asthma that has the concept of effective communication, collaboration, and personalized goal setting as a means to help reduce primary care and emergency department visits (Figure 2).[40]

## Tailoring consultation style toward patient preferences and shared decision making

Clinicians should aim to tailor their consultation style to the preferences, health literacy, and cognitive ability of each individual patient. A straightforward, but effective, way of opening a dialogue about patients' preferences is to request their feedback on their consultation.[41] Because poor health literacy is common and can often go undetected, it is good practice to ask patients to verbalize their understanding of any new concepts, using the aforementioned Tell-Back collaborative approach, to check comprehension, and to identify and correct potential misunderstandings.[42] *Shared decision making* can be defined as an active mutual partnership between the health care provider and the patient in which both parties share information, values, preferences, and decisions about treatment.[43,44] Shared decision making has been effective and cost-effective in patients with asthma,[45] but the approach may be preferred in younger, more educated individuals and in those with poorer adherence.[46]

**TABLE II.** Phrases to identify patients' self-reported medication adherence

Lots of people don't take their inhaler exactly as prescribed. In the last 4 weeks:
1. How many days per week have you been taking your [name of controller] inhaler?
2. How many times per day?
3. How many puffs do you take each time?

Thus, involvement in treatment decision making may not be appropriate to all and should be targeted appropriately toward those who are willing and able to participate.[46]

In consultations with children and their parents, it is important to elicit the child's perspective (asking, listening, acknowledgment of the child's opinion) as early as developmentally possible. Children 7 years or older are generally considered reliable reporters of their asthma symptoms and health status.[47,48] Patient-centered care and shared decision making can be successfully included in pediatric asthma management; for instance, the health professional can form a partnership with the parent that allows them both to share information and decision making with the child, appropriate to the child's developmental level.[49] Joint discussions with the child and the child' caregiver about respective responsibilities (eg, for medication administration, remembering to take it, and obtaining refills) are very important, particularly as adolescence approaches, because early engagement in asthma management will help prepare children for their inevitable responsibility in later adolescence and adulthood life.


**FIGURE 1.** Example of adherence counseling support tools. These adherence counseling support tools are designed to facilitate a flexible, personalized adherence discussion between a health professional and patient in a single, brief consultation. Patient's personal barriers to adherence with asthma preventer treatment (such as "Preventer concerns" or "Doubting chronicity") can be identified through the use of a brief, evidence-based asthma attitude questionnaire (see Foster et al[38]) and/or an empathic conversation that is accepting of non-adherence. The resource sheets shown in Figure 2 describe common reasons for poor adherence and common misconceptions. The general practitioner ticks off relevant topics to personalize the resource sheet, and provides it to the patient so they can discuss together the extent to which the information is relevant from the patient's perspective. For example, patients concerned about adverse effects of treatment may overlook the adverse effects of poor medication implementation or persistence, for example, being unable to do the things they want to in life due to asthma symptoms or exacerbations. According to the principles of motivational interviewing, encouraging the ambivalent patient to talk about the benefits (as well as the down sides) of treatment can help them decide to adhere to prescribed treatment. From Foster et al,[38] reprinted with permission. *GP*, General practitioner; *MICA*, Management to Improve the Control of Asthma.

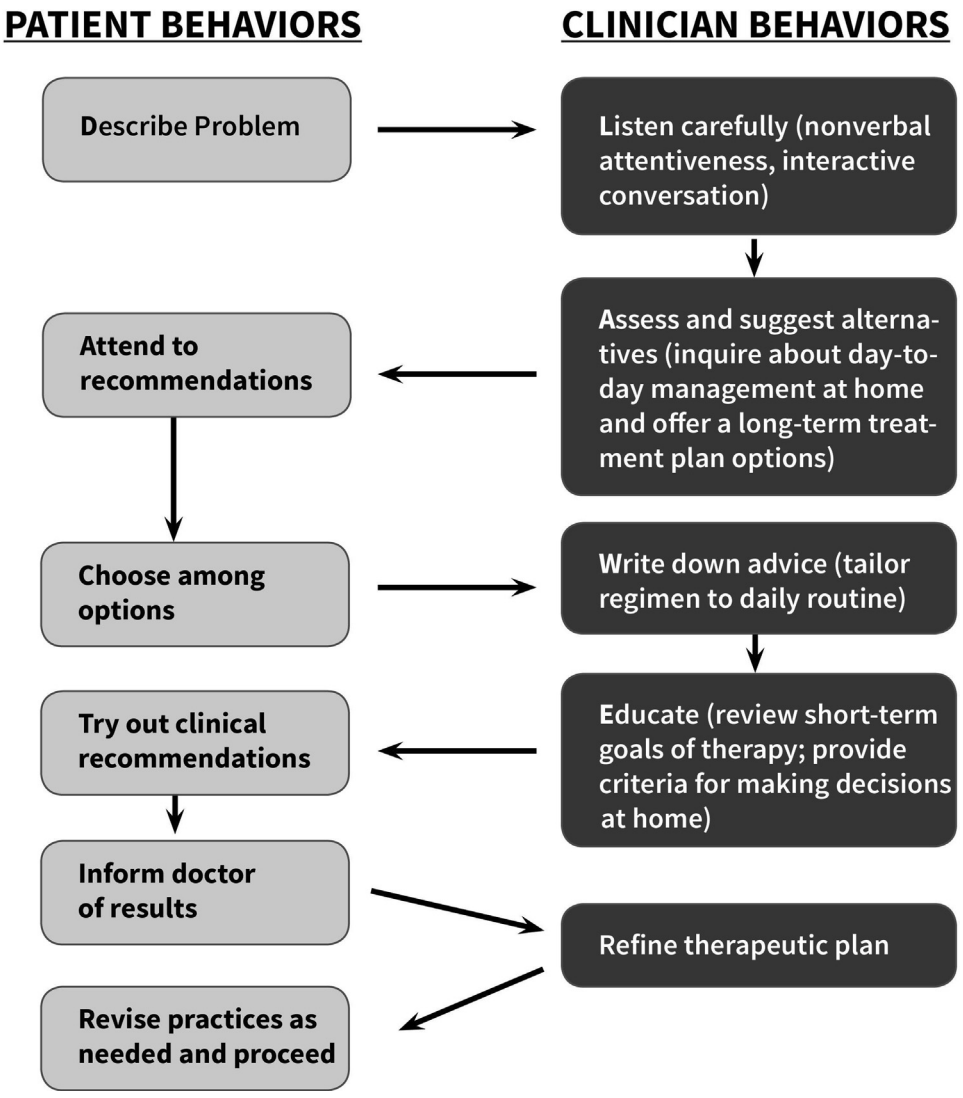


**FIGURE 2.** Model of clinician-patient partnership in asthma.[40] From Clark et al,[40] reprinted with permission from SAGE Publications, Inc.

## Role of the community pharmacist

Primary care physicians offer a well-trained and familiar resource from which patients can seek guidance about their condition and treatment. Yet primary care resources are under pressure owing to ever-increasing demand and respiratory care remains suboptimal.[50] In such resource-limited scenarios (and more generally), community pharmacies can complement and reinforce existing primary care—led support services to improve all aspects of medication adherence and decrease hospitalizations.[51]

The accessibility of community pharmacies is a key to the role they can play in supporting primary care services. In the United Kingdom alone, 438 million visits are made to community pharmacies each year for health care— related reasons—more visits than are made to any other health care setting in the country.[52] Community pharmacies offer patients a unique set of service features, which positions them well to support patient care.[53] These features include their specific training on optimal selection and use of pharmacotherapy, geographical distribution (including in deprived areas), position as a trusted health care professional,[54] and flexible opening hours (particularly evenings and weekends). Furthermore, for those patients who use a regular pharmacy, there is opportunity to build patient-pharmacist rapport, to support patients, and capture longitudinal medication adherence data to identify potential noninitiation, suboptimal implementation, and potential discontinuation.

Although there are inherent limitations to providing support at the point of dispensing (eg, lack of privacy) and in the context of potential commercial operational drivers, the role of the pharmacist is important across all steps in the medication adherence pathway, in setting expectations around treatment use at the time of initiation, providing device training to support medication implementation, and in terms of medication usage reviews to assess persistence and identify discontinuation.[55]

## Specific pharmacy tools

Pharmacies usually save each patient's drug history to a unique patient medication record, which, along with their dispensing history, pharmacists can use to identify patients in need of potential support[56]; for example, a patient with asthma who is overusing his or her reliever inhaler(s) and/or underusing his or her preventer

**TABLE III.** Expected clinical and economic effects of adherence-enhancing interventions for maintenance treatment in patients with asthma and COPD

| Focus of intervention | Intensity of use (eg, reminders, motivational interviewing, and education) | Quality of use (eg, inhalation technique) |
|---|---|---|
| Costs | | |
| Intervention costs | ↑ | ↑ |
| Medication costs | ↑ (maintenance), ↓ (reliever) | ≈ (maintenance), ↓ (reliever) |
| Other health care costs (eg, hospitalizations) | ↓ | ↓ |
| Effects | | |
| Beneficial pulmonary effects | ↑ | ↑ |
| Local adverse effects | ↑ (maintenance), ↓ (reliever) | ↓(maintenance) ↓ (reliever) |
| Systemic adverse effects | ↑ | ↑ |
| Beneficial extrapulmonary effects | ↑ (mainly in multimorbidity) | ≈ |

↓, Decrease; ↑, increase; ≈, similar.

inhalers can be identified.[57] Based on this principle, extended patient services, such as the Medicines Use Reviews and the New Medicine Service, have been developed in the United Kingdom for adoption by community pharmacies.[58] These services offer pharmacists financial incentives to provide patients with additional care. For those patients who do not attend primary care, pharmacy Medicines Use Reviews could be beneficial in tailoring treatment and optimizing all aspects of medication adherence. Existing dispensing software allows for brief, cost-effective, and tailored interventions.[55,58] Simple advice, such as advising patients about common adverse effects, and how to manage them, can have a significant impact on medication adherence.[58]

As frequently visited health care "hubs," community pharmacies have the potential to monitor adherence, to intervene as appropriate, and to capture valuable refill data for use in adherence research. Their role in optimizing medication adherence (eg, "timely" initiation assessments and extent to which physician-issued prescriptions are collected by patients) and patient care can be greatly enhanced through good communication and coworking with primary care physicians[59] and by combining physician-prescribing data with pharmacy refill data to inform more robust assessments.

## PRIMARY CARE–BASED ADHERENCE INTERVENTIONS IN ASTHMA AND COPD

Now we describe some examples of adherence interventions suitable for primary care or community settings.

### Clinician communication skills

A randomized controlled trial (RCT) in the United States trained primary care physicians on asthma guidelines, communication techniques, and key educational skills for use in pediatric consultations. Use of these skills was associated with a significant improvement in patient-reported physician communication skills and improved patient health outcomes (days limited by asthma symptoms and number of annual emergency department visits) compared with the control group.[60]

### Patient communication skills

In an observational study, Butz et al[61] provided communication training and support tools for use in home visits by nurse/health educators to school-aged children with asthma and their parents to improve children's communication during nonurgent primary care visits. Although no preintervention baseline data or control group was included in the study (limiting the interpretation of the results), children were observed to participate actively in the consultation after training, with 83% personally reporting their asthma symptoms and 75% talking about their personal goal for asthma after prompting from a parent/nurse.

The effect of facilitated asthma communication intervention (FACI) was also evaluated in an RCT involving more than 300 low-income preschool children in the United States.[62] FACI and FACI delivered via a mobile medical clinic (Breathmobile) were compared with standard asthma care. Both FACI interventions were designed to remove common barriers to asthma care: the Breathmobile by overcoming structural barriers (transportation, access to care, and health insurance status) and FACI by empowering families to communicate with their physicians more effectively. Although neither FACI intervention strategy resulted in a statistically significant improvement in asthma management or asthma morbidity at 12 months (compared with usual care), children in the Breathmobile + FACI group had a 6.6% increase in symptom-free days at 6 months. These findings suggest that more research is needed to evaluate community interventions that may result in meaningful and sustainable clinical outcomes.

### Adherence counseling

In a large Belgium-based RCT (n = 734), provision of extensive counseling to patients with COPD on inhalation technique and adherence at the point of dispensation and at 1-month follow-up resulted in statistically significantly higher inhalation scores and implementation measured by the proportion of days covered and lower hospitalization rates after 3 months (compared with the control group).[51] Positive results were confirmed in a similar, but smaller, 1-year RCT (n = 146) performed in Spanish primary care patients with COPD.[63]

### Adherence information feedback

The potential value of routine monitoring of asthma medication adherence, with feedback of this information to patients, for sustaining high levels of adherence has been assessed in a few small studies[64,65] and, more recently, in a large-scale practice-RCT.[66] Implementation of ICS therapy was estimated using combined prescription and refill data in patients with asthma

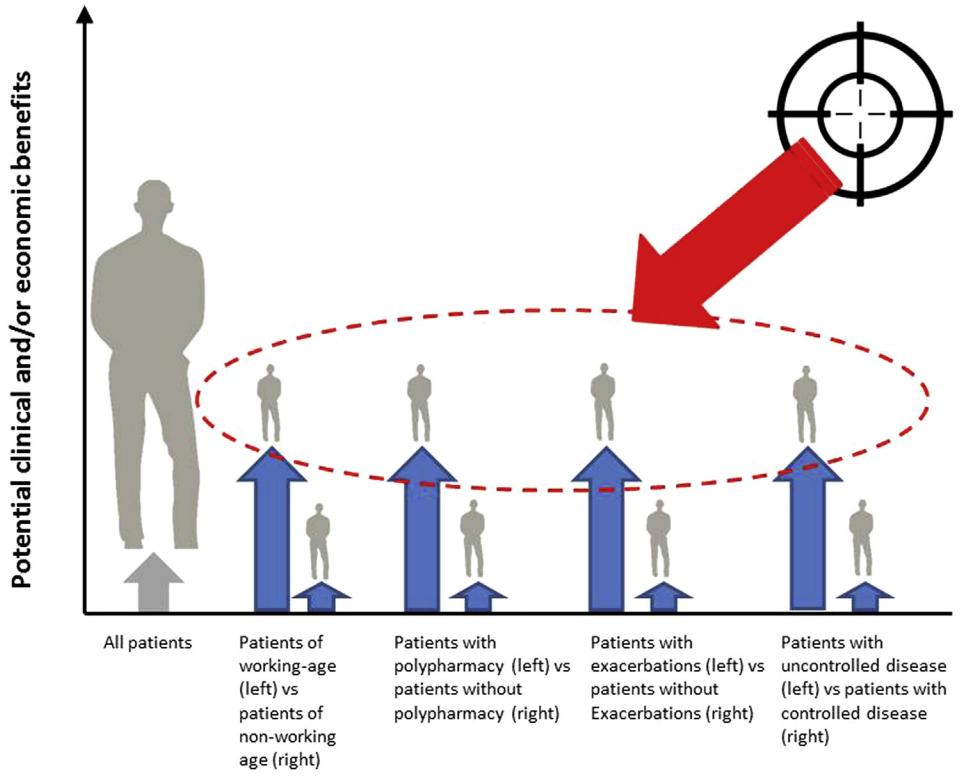


**FIGURE 3.** Potential clinical and/or economic benefits of targeting adherence interventions toward subgroups of patients with chronic respiratory disease with considerable room for improvement. As the diagram shows, benefits of adherence interventions are more likely to be observed if interventions are targeted at specific groups such as those working, taking multiple medications, experiencing exacerbations, or having uncontrolled disease.

aged 5 to 56 years. Clinicians in the intervention arm (compared with usual care) could view updated ICS adherence information on their patients via electronic prescription software. After 3 months, there were no significant differences in ICS adherence (implementation) among patients in the intervention arm and the control arm ($P = .553$). However, implementation rates *were* significantly higher among those patients in the intervention arm whose clinician elected to view their detailed adherence information compared with the control arm patients ($P = .026$) and compared with those in the intervention arm whose provider did not opt to view the detailed data ($P = .002$). The authors concluded that provision of adherence information to clinicians does not improve ICS use among patients with asthma, but that having a clinician who is sufficiently interested to access and view detailed data on his or her patients' medication use *can* support and improve medication implementation.

Reminder-based interventions may also help to improve adherence outcomes in primary care. A cluster RCT was designed to assess the effect of general practitioners providing their patients with twice-daily medication usage reminders for missed doses via an electronic monitor affixed to their preventer (again, a measure of implementation). The monitor also provided visual feedback of last dose taken and uploaded the patient's medication-use data to a Web page that both patients and their physicians could access to comonitor medication use. Over 6 months, average daily medication implementation in the intervention group was 27% higher than in the control group (73% vs 46%). Exacerbation rates were also lower in the intervention group compared with the usual care controls ($\geq$1 exacerbations, 11% vs 28%).[67] Similarly, COPD RCTs[68,69] report significantly higher adherence in active versus control groups (eg, adherent days, 60% vs 40%) who received electronic monitoring of ipratropium bromide plus feedback.[68]

## ROLE OF THE HEALTH CARE SYSTEM IN OPTIMIZING MEDICATION ADHERENCE

There are few studies investigating the impact of system's organization on adherence, particularly in respiratory disease, but the few studies that do exist indicate that the organization and structure of clinics and surgeries can affect adherence to asthma treatment. Organizational factors associated with improved adherence include fewer patients seen per hour, longer appointment length, evening consultation hours, multilingual staff, consistency of care, ease of making appointments, ease and effectiveness of telephone communication, and use of telephone calls for reminders and follow-up.[70] In contrast, increasing co-payments for visits and medication were associated with poorer adherence (where adherence was a generalized term in a systematic review involving 160 articles and encompassed reported adherence, compliance, noncompliance, and persistence).[71] More research is needed to understand how health care systems can be improved to better support medication adherence in asthma and COPD.

## COST-EFFECTIVENESS

The first prerequisite for adherence interventions to be cost-effective is a proper asthma or COPD diagnosis, along

**TABLE IV.** The International Primary Care Respiratory Group's adherence-related research priorities for asthma and COPD[96]

| Research category | Research need |
|---|---|
| Asthma | |
| Compliance | What is the impact of patients' comprehension of the disease, use of different treatment strategies, treatment cost (in high- and low-income countries and between social groups), and concern about adverse effects of inhaled steroids on adherence to prescribed treatment |
| Compliance | How may these issues of adherence be addressed (especially in subgroups such as the adolescent patient with asthma)? |
| COPD | |
| Self-management | What is the optimal format of self-management education (including the information content, individualization of the plan, written or electronic delivery, professional or lay educators) to ensure effective communication with patients (often from deprived communities), facilitation of adherence to treatment, and a positive impact on health status? |

with appropriate prescribing of pharmacological and/or non-pharmacological treatment. Second, better use of existing respiratory therapies may be more cost-effective than investing in new technologies.[72] However, the extent of cost-effectiveness of any given intervention is largely dependent on the macroeconomic burden of the disease it is intended to treat and is likely to vary depending on the condition, country, and context in which therapy is used. For example, an intervention may appear feasible for both asthma and COPD, but may be cost-effective only when used in patients with COPD or in an asthma subpopulation.[73]

## Cost-effectiveness of adherence management in COPD

Before assessing the cost-effectiveness of adherence interventions in patients with COPD, it is important to first establish the overall economic burden of COPD to identify the potential economic gain of different management approaches. For example, in the Netherlands, evaluation of the macroeconomic burden of COPD reveals that approximately 35% of the total national costs of COPD are incurred as medication costs[74] whereas the other 65% are mainly incurred through hospitalizations and health care consultations. In other countries, cost patterns may be very different. Notably, nonadherence (non-initiation, poor implementation, and early discontinuation) in COPD is associated with worsened clinical and economic outcomes, specifically higher rates of hospitalizations and exacerbations and greater mortality and work productivity losses.[75-77] Interventions targeted at improving medication adherence (any or all steps of the pathway) may be able to improve clinical outcomes and reduce associated costs. The initial cost of the adherence intervention (and its associated medication) may be offset by the intervention's ability to reduce rates of costly events (eg, hospitalizations).[78] Studies that assess the cost-effectiveness of adherence interventions in COPD are scarce, but those that exist do suggest favorable cost-effectiveness.[78,79]

**TABLE V.** Proposed adherence research needs within the health care system and health economic domains

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|---|
| Health care systems (including health care professionals) |
| • Design and uptake of integrated system-level (multilevel) interventions that work across multidisciplinary teams:<br>  ○ Simple global models that can be tailored to local settings |
| • Development of a framework and models to underpin defragmentation and integration of data across different health care assets (eg, integration of pharmacy data, primary and secondary care data, and patient-reported outcomes) |
| • Validation of adherence profiles defined through electronic medical record (eg, pharmacy and prescribing refill data)-based research |
| • Development of methods and models to improve the engagement of health care professionals (and providers) in the promotion of medication adherence to their patients (and clients) |
| • Assessment (and provision) of appropriate knowledge, skills, and attitudes within the health care system to facilitate optimal adherence |
| • Evaluation of the effect of medication changes on treatment adherence and future risk |
| • Development of core variables that E- and M-Health applications should collect to ensure the availability of valuable data for future adherence research |
| • Evaluation of the potential for artificial intelligence and machine learning to inform and guide adaptive care delivery to optimize adherence and clinical outcomes |
| • Evaluation of the cost-effectiveness and scalability of adherence interventions (to aid in their promotion and successful uptake) |
| Health economics and scalability |
| • Development of standardized health economic measures for use in cost-effectiveness modeling of respiratory adherence interventions |
| • Improved reporting of the methods used in health economic modeling of respiratory adherence research |
| • Multifactorial analysis approaches for the evaluation of cost-effectiveness of adherence interventions |
| • Evaluation of the real-world (cost)-effectiveness of licensed respiratory therapies |
| • Development of research methods to identify target populations in whom adherence interventions will be most cost-effective |

## Cost-effectiveness of adherence management in asthma

Similar to COPD, suboptimal adherence to asthma medication has been shown to be associated with poor clinical and economic outcomes.[80] Yet, in many countries, the macroeconomic burden of asthma differs considerably from that of COPD. In the Netherlands, medication costs account for 65% of the total national asthma expenses (in contrast to 35% in COPD) and this high proportion of medication costs limits the extent to which adherence interventions can reduce the total national expense for asthma.[74] Hospitalization is a large expense, but, at least in countries with well-developed asthma care, baseline hospitalization rates in asthma are low (±4%), leaving little opportunity to decrease total asthma costs significantly through better adherence (and resultant improved clinical outcomes) alone.[81] Decreased national costs for asthma could therefore be achieved only by better adherence *and* decreased unit cost of medication. Therefore, although improvement in Global-Initiative-for-Asthma–defined symptom control has been shown to reduce direct asthma-related health care costs,[82] the cost-effectiveness of increasing medication intensity is equivocal.[83] In countries where asthma care is less developed or in countries with limited health insurance or social

security, hospital costs or the impact of asthma on family income can be relatively much higher.[84] Consequently, asthma adherence interventions have greater potential to be cost-effective in those countries.[73,84] Interventions targeted at improving inhalation technique, however, may offer greater cost-effectiveness in countries with high medication costs as a proportion of asthma total cost. Improved inhalation technique promotes more effective outcomes from an existing medication, which can reduce costs through, for example, lower prescribing of add-on medications or high strength inhaled steroid therapy (Table III). Unfortunately, we could not find any published, well-performed cost-effectiveness studies on this specific topic.

## Targeting of interventions

To maximize outcomes and cost-effectiveness, the appropriate targeting of interventions should be considered. Targeting aims to identify subgroups of patients who stand to benefit most from a specific intervention, in either clinical and/or economic terms, and to prioritize use appropriately. Adherence interventions should be effective for the appropriate step of the adherence pathway (initiation, implementation, or persistence) and applied only in patients with suboptimal adherence behaviors as identified a priori. From a principally cost-effectiveness perspective, further targeting of the use of interventions may be guided by the intervention's ability to reduce high-cost health care resource utilization (eg, severe exacerbations) and/or to minimize the socioeconomic impact of disease (eg, in working age patients) (Figure 3).

**Identifying patients with poor adherence and/or at high risk of exacerbation.** As previously mentioned, pharmacy refills (or prescription renewals in the clinic) could be used to identify nonadherent, potentially at-risk patients with COPD[85] or asthma,[57] helping to target interventions at those with the greatest to gain from the intervention. Validated patient questionnaires such as the Asthma Control Test or the Asthma Control Questionnaire could be used to identify and target patients with uncontrolled disease because, especially in those with uncontrolled asthma (Asthma Control Test score <20), fewer exacerbations are associated with higher rates of medication adherence.[86]

**Targeting patients with comorbidities and polypharmacy.** Patients with COPD tend to suffer from multiple comorbidities and are dependent on use of polypharmacy. Research indicates that interventions focusing on adherence to COPD medication may also result in beneficial extrapulmonary effects in patients with COPD, possibly due to more healthy patient behavior (eg, lifestyle changes and better adherence to comedication).[78] Indeed, counseling and education on the benefits of adherence to one prescribed therapy results in improved adherence to comedication.[87]

**Targeting patients of working age.** Although direct health care costs are usually somewhat lower in the working age asthma population, indirect costs (such as lost productivity) contribute substantially to the overall societal burden of chronic conditions such as asthma.[88] Model-based approaches often suggest equivocal cost-effectiveness of adherence interventions in asthma, but when reduction in lost productivity is included they can offer economic benefit.[83] Also, in COPD, indirect costs (lost and impaired productivity) exceed direct medical costs in the working age population, indicating the potential for cost-effectiveness of adherence interventions.[89]

**Targeting interventions to high-risk periods.** In COPD, exacerbations are up to 4 times more frequent in winter than in summer months[90,91] whereas in infants and school-aged children with asthma, severe exacerbations are more frequent in winter or at return to school, respectively. Using interventions before/during critical seasonal periods may result in a more concentrated effort, a greater reduction in exacerbation frequency, and better relative gains and increased cost-effectiveness,[92] although clinically and behaviorally it may be preferential for patients to establish a consistent daily medication-taking routine.

## Target, but do not forget to tailor

Beyond targeting, it remains essential that interventions are selected and tailored to the individual needs of the patient. For example, patients who fail to initiate, implement, and/or persist with therapy because of specific beliefs about treatment (eg, adverse effect concerns) are unlikely to benefit from treatment reminders. Therefore, identifying adherence patterns and investigating the reasons for these patterns remain essential. Emerging technologies such as "Smart Inhalers" can provide real-time insight into patients' unique medication-use pattern including evidence of suboptimal inhalation technique.[93-95] Systematic approaches for the recording of patients' unique medication adherence barriers and communication techniques to address these are also emerging in the adherence literature.[37,38] Ongoing and future research into the potential role of such technologies will help inform and guide their optimum use. Last, some adherence interventions (eg, automated texting programs and sending letters to patients who do not refill their medications) can be very low cost, whereas others (eg, case managers who reach out to patients with recent exacerbations) are usually more costly. Tailoring therefore may include directing more cost-intensive programs for those patients who have been hospitalized for their asthma or COPD.

# CONCLUSIONS

Health care professionals—clinicians, nurses, and pharmacists—have a key role to play in engaging and educating respiratory patients on the potential benefits of treatment, monitoring adherence, and in providing ongoing education and inhaler technique training. Health care professionals should be conscious of the range of factors that can facilitate (or inhibit) medication initiation, implementation, and persistence (ie, adherence), such as use of appropriate consultation skills, language, collaborative goal setting, and continuity of care.

From a health care cost perspective, improving adherence (all steps) can be economically viable for patients with asthma and COPD, but cost-effectiveness estimates differ substantially between these conditions, between countries, and also across subpopulations. Moreover, targeting adherence interventions at patients with the greatest to gain from available interventions may help to improve cost-effectiveness.

Looking forward, research efficiencies can be achieved through identifying and addressing priority adherence-related research needs such as those published by the International Primary Care Respiratory Group (Table IV).[96] The central role that the relationship between patients and their health care professionals can play in achieving more tailored and individualized care has been emphasized in this review, but more work is required to quantify the benefit of some of these approaches, such as SIMPLES. Therefore, additional research needs are proposed in Table V—a reflection on some of the system-level, cost-effectiveness, and

scalability issues discussed in this review. Addressing these needs is expected to further improve medication adherence and quality of life of patients with asthma and COPD in a cost-effective manner.

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